214 | Allergic Drug Reactions

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Definition

An *adverse drug reaction* (ADR) is an undesired and unintended response to a drug that occurs with usual therapeutic doses. Hospitalized patients receive an average of 6 to 10 drugs, and ADRs may occur in up to 15% of this population. An *allergic drug reaction* is one involving the special biochemical mechanisms involved in immunologic amplification. Fewer than 15% of all ADRs are allergic in nature. The different types of ADRs are summarized in Table 214.1.

Care must be exercised in defining an allergic reaction. In particular, an immunologic explanation for an untoward event cannot be accepted merely because other explanations are lacking. Even with such care, exact definition often remains difficult, because rechallenge with the suspected agent is usually unethical. Some features that support an allergic mechanism are as follows:

- The reaction takes a form associated with known immunologic mechanisms, e.g., rash, urticaria, anaphylaxis, serum sickness.
- The reaction cannot be explained on the basis of known pharmacologic or idiosyncratic effects of the drug(s).
- In the absence of prior exposure, the reaction occurs after 7 to 10 days on the drug. With prior sensitization, an anaphylactic reaction usually occurs within 30 minutes and other "accelerated" reactions within 2 to 4 days.
- Other features, such as eosinophilia and resolution on withdrawal of the drug, support the diagnosis.
- In the case of drug fever, the patient often appears remarkably well despite the height of the fever. This may be explained by the release of endogenous pyrogen (interleukin I) in the absence of toxemia or septicemia.

Table 214.1
Classification of Adverse Drug Reactions

Pharmacologic
Exaggeration of desired therapeutic effects, e.g., oversedation with opiates[a]
Undesired effects, e.g., nausea with opiates[a]
Drug interactions[a]
Secondary effects such as release of "endotoxins" from organisms killed by antimicrobials, e.g., Jarisch-Herxheimer reaction
Intolerance: undesired pharmacologic effect with small doses of the drug
Idiosyncrasy: abnormal pharmacologic effect due to a biochemical difference in the host, e.g., primaquin-induced hemolytic anemia in G6PD deficiency
Immunologic
These reactions are also chemically mediated but are characterized by exponential *amplification* of responses initiated by very small doses of antigen following *specific* immunologic recognition, e.g., mast cell degranulation, complement activation, or lymphokine release
Immunelike
These reactions occur when amplification of immune responses is not initiated by a specific antigen but by nonspecific modulators, e.g., mast cell degranulation by opiates or by radiopaque dyes. Alternatively there may be hyperreactivity due to loss of control over immune amplification, e.g., angioedema in C1 esterase deficiency.
Adverse nondrug reactions
Patients may experience undesirable events while on drug therapy but not caused by the drug, e.g., fainting, nausea, diarrhea, viral skin rash. In one series these were reported in 20% of hospitalized patients.

[a]As these types of effects are largely dose related, the risk is predictable and can be reduced by careful titration of the dose and monitoring of patient responses.

Technique

As can be seen from Figure 214.1, there are a finite number of immunologic response mechanisms, although any one drug may activate one or more of these types. Also, the body has a limited number of ways in which it can express the inflammatory consequences of immunologic amplification. Thus, unlike pharmacologically mediated reactions, what we observe clinically is not the effect of the drug itself but the limited number of immunologic and inflammatory reactions to the drug. For all these reasons, it is seldom that a particular allergic reaction is pathognomonic of a particular drug. The history of the temporal relation of drug administration to the occurrence of the reaction is thus the single most powerful diagnostic tool at our disposal.

The diagnosis of adverse drug reactions rests with a careful history detailing the composition of the offending drugs, including their nonpharmacologic additives (e.g., tartrazine dye) along with the sequential temporal relationship of the development of the undesired effect to the administration of the drug(s). Apart from the unlikely option of rechallenge, tests in vivo and in vitro are to be regarded as *correlates* of the diagnosis and do not themselves "make" the diagnosis. For example, a positive skin test does not prove an etiologic role in the allergic event. Nor does a negative skin test exclude an allergic relationship that may be mediated by a degradation product of the drug or by immunologic mechanisms not revealed by skin testing. Hence, all tests, positive or negative, must be interpreted in the context of the history, with particular attention to the following:

- List *all* drugs and route(s) of administration taken by the patient that can be recalled. Ideally this should include agents taken years before.
- Construct a table listing *all* ingredients of all medications including the pharmacologically inert compo-

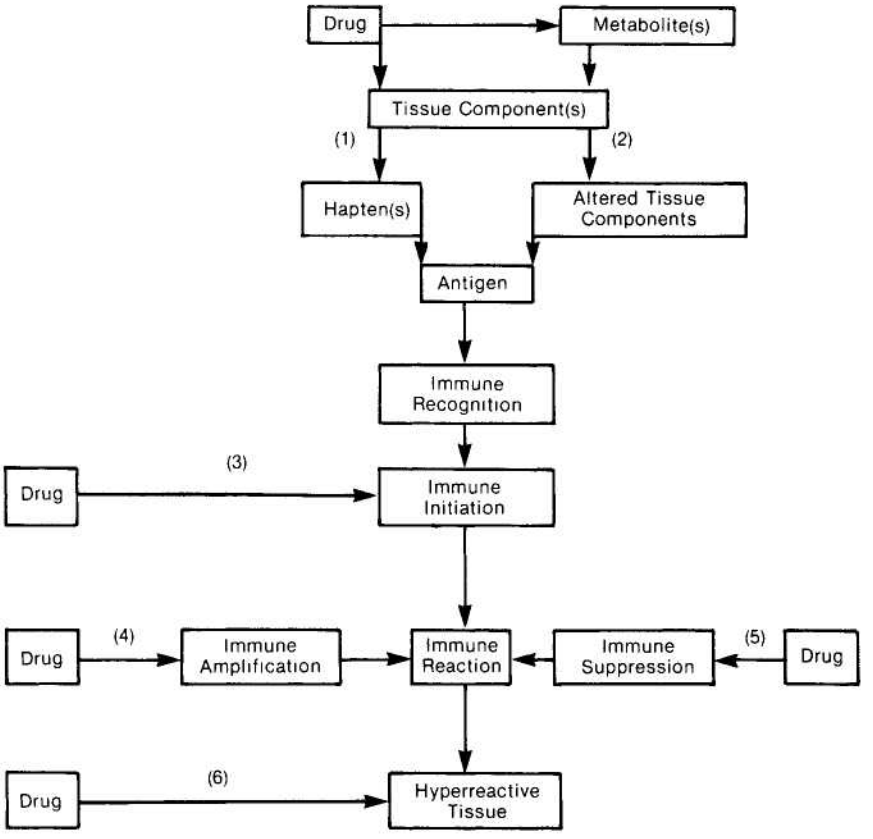

Figure 214.1
Some of the points at which drugs may act in causing damaging immunologic reactions.
(1) The drug or its metabolite(s), after combination with a blood or tissue component, can become allergenic.
(2) The drug or its metabolite(s) may alter tissue component(s) so that the tissue becomes immunogenic, e.g., procainamide-induced lupus.
(3) The drug may initiate immune amplification chemically without the need for specific immunologic memory and recognition, e.g., mast cell degranulation by radiopaque contrast media or opiates.
(4) The drug-antibody complex may "hop" from cell to cell leaving activated complement behind to lyse the cell, e.g., Type III immune complex induced hemolytic anemia in which the direct Coombs test is positive for complement only on the red cell.
(5) The drug may augment immunologic amplification by blocking suppressor T cell activity, e.g., augmented delayed type hypersensitivity (DTH, Type IV) reactions by cyclophosphamide and dextran.
(6) The drug may act directly on hyperreactive tissues, e.g., bronchospasm initiated by aspirin (via effect on prostaglandins) or by "irritation" by inhaled polymyxin or Cromolyn.

nents such as filler, dyes. For example, an allergic reaction to procaine penicillin may be due to allergy to penicillin or to "caine" anesthetics. The age of the drug should also be included, as the shelf life may have been exceeded by many years. The chemical nature of the drugs should be carefully analyzed, as drugs in different therapeutic classes may belong to the same chemical family (e.g., sulfonamide antimicrobials and sulfonyl urea hypoglycemics or lidocaine as an antiarrhythmic or local anesthetic).

- Analyze the table for prior administration of the same or similar clinical components (e.g., any member of the penicillin or sulfonamide families).
- Document the time interval(s) between administration of the drug(s) and the development of the untoward event. As stated, anaphylactic reactions usually occur within 30 minutes. Other immunologic reactions usually take 7 to 10 days to develop. This latter time frame represents the need for clonal expansion of the reactive B and/or T lymphocyte populations. The exception to this time scale is patients with prior exposure to the drug, in whom a so-called accelerated reaction may occur in 2 to 72 hours. Some patients may not recall prior administration of a drug, however, or it may have been received unwittingly from a relative or physician or in foods contaminated by drugs.
- Document the description of the untoward event carefully so as to exclude recognized pharmacologic effects of the drug(s) and to confirm that the event corresponds with recognized patterns of immunologic reac-

tivity. This will include persistence or worsening with continued administration (or with drugs with long half-lives) and improvement on discontinuation.

Basic Science

This chapter does not provide an encyclopedic treatment of all allergic drug reactions. Instead, a problem-solving framework with examples is provided that will assist the reader in understanding, anticipating, diagnosing, and preventing such reactions. Before addressing this objective, it is important to deal with some widely held misconceptions.

1. Adverse drug reactions are *not* to be regarded as nuisance events that only occasionally complicate patient management. Just as there are no roses without thorns, ADRs are an inevitable consequence of therapeutic intervention with drugs. In the United States, over 750,000 hospitalizations per year result from ADRs at an estimated cost of thousands of millions of dollars.

2. The great majority (>80%) of ADRs are pharmacologic (*not* allergic) in nature and follow the dictates of pharmacologic dose/response curves, that is, the higher the dose, the greater the various effects. In achieving these pharmacologic effects, the drug is neutral, and it is we who decide what is "desirable" or "undesirable."

3. The term *allergic* ("other reacting") is misleading and suggests some almost magical process. In reality, the biochemistry of immunologic processes is arranged so as to provide *exponential amplification* of the response as exemplified by mast cell degranulation, the complement "cascade," or release of lymphokines by lymphocytes. Immune amplification is clearly necessary in dealing with the challenge of rapidly self-replicating antigens (e.g., viruses, bacteria, or tumor cells), which, if unchecked, threaten to take over the physical space occupied by the body of the host animal. Unfortunately, these same responses can initiate inflammatory reactions that are injurious to the tissues.

4. The term *antigen* should not be allowed to conceal the fact that all antigens are merely chemical entities, however complex they may be. Thus, given the "universality" of biochemistry, it is not surprising that immunologic amplification can occasionally be initiated by molecules that mimic immunologic mediators or share the chemical configuration of antigens and/or antibodies. For example, histamine release from mast cells is "normally" mediated by the cross-linking by bivalent antigen of IgE molecules that have previously adhered to the surface of the cell. But the same effect can be initiated by iodine-containing radiopaque contrast media or opiates. Similarly, lymphokines can be released from lymphocytes by exposure to nonspecific plant extracts (lectins) such as concanavalin A. The well-known gastrointestinal intolerance to beans and gluten enteropathy may be mediated by such nonspecific (i.e., nonantigenic) triggering of immunologic amplification. In this light, the long-debated difference between gastrointestinal allergy versus intolerance to foods and drugs becomes less confusing.

5. The still convenient Gell–Coombs classification of hypersensitivity reactions into four types (I through IV) is now conceptually outmoded, as is the division of immune responses into humoral and cell mediated. As antibodies are produced by B lymphocytes and lymphokines by T lymphocytes, all immunologic reactions are, in a sense, cell mediated. Table 214.2 is an attempt to reconcile both of these older classifications into a more meaningful functional form.

Table 214.2
Classification of Immunologic Drug Reactions

	Cell bound antigen	"Free" antigen	No antigen
Cell bound antibody	ADCC and Type V	Type I	—
Free antibody	Type II	Type III	—
T cell mediated	Type IV	Type IV	—
No antibody	—	—	Immunelike

ADCC = Antibody dependent cell cytotoxicity where antibody attachment to the target cells is followed by killing of the cells by lymphocytes, macrophages, or polymorphonuclear cells.
Type V reaction = Cell stimulation by antibody, e.g., thyroxine release by IgG long acting thyroid stimulator (LATS).
Type I = Mast cell degranulation by IgE in the presence of antigen.
Type II = Antibody attachment to drug hapten on cell surface. The cell is then removed by the spleen or lysed via the participation of complement.
Type III = Formation of antigen-antibody complexes which fix complement. These complexes then damage "innocent bystander" cells, e.g., red blood cells or vascular endothelial cells.
Type IV = T cell mediated via lymphokine release, e.g., PPD skin reaction or contact dermatitis.
Immunelike = immunologic amplification not initiated by specific antigen (as defined by specific immunological memory) but by nonspecific chemical means, e.g., mast cell degranulation by radiopaque dyes or lymphokine release stimulated by lectins in plants and foods.

As an example of the possible points of interaction of a drug with the immune system, allergic reactions to penicillin can be mediated via reaction types I, II, III, and IV.

6. It is important to distinguish the emerging classification of the difference between the chemistry of immunologic amplification in response to antigen and the chemistry of *tissue hyperreactivity* to the end products of such amplification. For example, for a patient to have "allergic asthma," he or she probably must be both "allergic" to antigen *and* have hyperreactive bronchi as defined by hyperreactivity to an intrabronchial challenge with methacholine. As soon as this double requirement is appreciated, some of the clinical confusion about allergic reactions vanishes. It also follows from this concept that the immunologic event may occur at one anatomic site with the hyperreactive organ in another. For example, in a recent study it was shown that, in some cases of migraine precipitated by food, ingestion of the offending food led to increased IgE-containing immune complexes. In this case, the immunologic amplification occurred in the gut with the hyperreactive target organ in the cerebral blood vessels. The occurrence of migraine and the appearance of the immune complexes in the blood could be prevented by oral Cromoglycolate.

7. The above discussion relates to immunologic reactions directed at the drugs or their metabolites. It will also be obvious that a drug, by its chemical nature, can alter the host tissues so that they themselves become antigenic and elicit an autoimmune reaction via any of the mechanisms described in Table 214.2. One example of this includes procainamide-induced systemic lupus erythematosus (SLE) due to alteration of components of the cell nucleus so that antinuclear antibodies appear, but *not* antibodies to *native* DNA.

In conclusion, the conceptual sequence of immunologic initiation by specific or nonspecific means, leading to inappropriate immunologic amplification followed by inappropriate tissue reactivity, provides a rational framework for understanding "allergic" events. For a fuller (but read-

able) account of these immunologic mechanisms the reader is referred to the excellent reviews by Platts–Mills (1982), Henson (1982), and Henny and Newman (1982).

Testing for Drug Allergy in Vivo and in Vitro

Because of the dangers of documenting drug allergy by readministration of the drug, a great deal of attention (usually unsuccessful) has been devoted to the development of less hazardous tests. As a basis for approaching this problem, Figure 214.1 illustrates the points at which drugs may act in order to invoke the processes of immune amplification and tissue reactivity. From this diagram, the principles and limitations of tests for drug allergy are self-evident. First, although administration of a drug may give rise to an allergic event, it may be a metabolite of the drug that is actually responsible (e.g., penicilloyl polylysine or the so-called major and minor determinants of penicillins). Second, immunologic responsiveness is common to all hosts and, apart from dealing with rapidly self-replicating antigens, is also involved in clearing the body of foreign material. For example, a "mild" local reaction to pollens in the eyes may have the beneficial effect of increasing the flow of exudate and enhancing removal of the pollen. If the reaction is strong enough to produce clinically obvious inflammation, the patient is then declared to be "allergic," as if this were an all-or-none event. Third, clinical allergic events may result not only from initiation of immune responses by drug haptens or by autoantigens in drug-altered tissues but also from failure of suppression (i.e., control) of immunologic amplification or from target organ hyperreactivity to normal levels of immunologic mediators. Thus, for a patient to have allergic asthma, he or she probably must have two problems: "allergy" to antigen and hyperreactivity of the bronchial mucosa and smooth muscle to the end products of immunologic amplification.

It follows that drug hypersensitivity may result from action of a drug at one or more of the points of the sequence shown in Figure 214.1. Unfortunately, the absence of precise sequential kinetic studies of the causation of the various allergic reactions to drugs makes extrapolation of the results of tests in vivo and in vitro problematic. Thus, just because a drug degranulates mast cells or releases lymphokines from T lymphocytes does not necessarily mean that this is the mechanism of tissue damage. For the same reason, even a positive immediate (Type I) or delayed (Type IV) skin reaction cannot on its own be taken as absolute evidence but must be interpreted in the context of the overall clinical picture. With this in mind, we can now examine the usefulness of various tests in vivo and in vitro.

RECHALLENGE

It will be clear from Figure 214.1 that the only way totally to imitate the alleged allergic reaction is to readminister the same drug, under the *same brand formulation*, at the same dose by the same route. This is usually unjustifiable except under very unusual circumstances (e.g., acute life-threatening infections where the drug is the only viable therapeutic option). If absolutely necessary, the process is undertaken beginning with approximately $1:10^5$ dilutions of the usual therapeutic doses. Epinephrine (already drawn in a syringe) and means for intubation, tracheostomy, and life support should be available in experienced hands.

TESTS OF DERMAL REACTIVITY

Type I Reactions. For this purpose, a small dose of the drug is injected intradermally and the result read after 15 to 30 minutes. The appearance of inflammatory edema and redness (i.e., wheal and flare reactions) follows drug-induced degranulation of mast cells in the skin as a result of bridging of two IgE molecules by *divalent* antigen. As most drugs have a molecular weight below 1000 daltons, they are not usually antigenic on their own, far less antigenically divalent. Exceptions are high-molecular-weight agents such as horse antiserum; vaccines containing egg protein (e.g., influenza vaccine); hormones such as insulin, adrenocorticotrophic hormone, and pitressin; dextran; whole blood products; local anesthetics; and diagnostic agents such as bromsulphthalein and radiopaque contrast media. It should be noted that opiates (e.g., codeine) may release mast cell mediators directly (i.e., nonimmunologically), thus producing a "positive" skin test.

The only low-molecular-weight drug for which reliably standardized immunologically mediated skin testing can be carried out is *penicillin.* Penicillin becomes allergenic by forming drug-protein complexes. The allergenic degradation products of penicillin are referred to as "major" (more frequently responsible) and "minor" (less frequently responsible) determinants. However, the "minor" determinants can precipitate major clinical reactions. The major determinant is tested by means of a synthetic penicilloyl-polylysine (Pre-Pen) that cross-links with IgE on the mast cell but does not itself stimulate IgE production (i.e., is not immunogenic). However, because of its reactions with sensitized mast cells, Pre-Pen can itself precipitate anaphylaxis. The minor degradation determinants are not commercially available, but dilute concentrations of newly reconstituted penicillin solutions and "old" solutions reconstituted 1 week before can be substituted. See DeSwarte (1980) and Mellon et al. (1981) for detailed protocols of administration and interpretation of such tests.

The principle of testing is to begin with intradermal prick testing using dilute (e.g., 10 units/ml) solutions of penicillin in physiologic saline. If this is negative, proceed with intradermal injections of 0.02 ml penicilloyl-polylysine and the minor determinants in incremental concentrations. This testing must take place with epinephrine drawn into a syringe with resuscitative measures for endotracheal intubation or even tracheostomy readily available.

In the series of Green et al. (1977) the results of testing were as follows: with a negative history of penicillin allergy, 7% of subjects yielded positive skin tests; with a positive history, 19% had positive reactions. This illustrates that the patient's recollections may not be reliable and/or that the degree and type of immunologic reactivity may vary with time. Thus, 75% or more of patients with a positive clinical history may take penicillin later without event. Even when the dramatic and unforgettable marker of anaphylaxis to penicillin was used, only 40% of such patients had positive skin tests. The corresponding figures for prior urticaria (17%) and rash (7%) are also remarkably low. Finally, when nine patients with positive skin tests were therapeutically challenged, six reacted, of whom three had immediate (<30 min) or accelerated (2 to 72 hr) reactions. When 346 patients with negative skin test reactions were treated with penicillin, fewer than 1% had immediate (IgE) reactions and another 2% had other reactions. Thus a negative skin test may indicate a relatively low risk of clinical reactivity. A positive test indicates very careful weighing of the therapeutic benefit–risk ratio. Other types of allergic reactions to the

penicillins mediated by IgG and IgM (e.g., hemolytic anemia, interstitial nephritis) are described in the sections dealing with specific organ involvement. These types of reactions are not predictable by skin testing with Pre-Pen and the major and minor determinants.

A similar approach is applicable to skin testing for reactivity to *local anesthetics*. These drugs can be divided into two groups, depending on possession (i.e., benzocaine, procaine, etc.) or absence (e.g., dibucaine, lidocaine) of a paraamino phenyl group. The potential for adverse effects may differ between the two groups. Although the mechanism of such effects is not clear, Type I (IgE-mediated) effects are probably rare. In this context, it is appropriate to note that drugs in different therapeutic classes may be chemically (and allergenically) similar. Examples include the use of procainamide and lidocaine in cardiac dysrhythmias and procaine in penicillin therapy. Occasionally one of these drugs may be mandatory despite a history of prior reactions to this group of drugs. If so, after a careful history, increased doses are given intradermally beginning with a prick test and working up to a 1.0 ml volume of undiluted material.

In the case of *radiopaque contrast media*, urticarial, bronchospastic, angioedematous, or full-blown anaphylactoid reactions are not initiated immunologically (Figure 214.1). Thus, skin testing is of no value. Consequently, if radiopaque contrast media examinations cannot be replaced by means such as CT or nucleotide scanning, the radiologic study is undertaken after premedication with steroids and antihistamines. As these cannot guarantee freedom from risk, however, the administration of the radiopaque contrast medium must take place with full resuscitative facilities available.

A similar situation exists in the case of urticaria, angioedema, and asthma induced by *aspirin*, where skin testing with aspiryl-polylysine may not discriminate reactors and nonreactors but may precipitate an attack. Such attacks are often associated with the presence of nasal polyps, but these are not pathognomonic for aspirin sensitivity. Again, aspirin reactions cannot reliably be ruled out by tests of bronchial hyperreactivity following intrabronchial challenge with histamine or methacholine. In this context, if the patient has a strong history, aspirin should be avoided, always bearing in mind that other nonsteroidal anti-inflammatory drugs can also precipitate asthma. If absolutely necessary, oral challenge with increasing doses of aspirin (beginning with 15 mg) on alternate days can be undertaken with fractional expired volume in 1 second measured before and at intervals up to 4 hours after ingestion of the challenge dose. A similar process can be followed in testing for tartrazine dye sensitivity.

Type IV Reactions. Theoretically, a delayed type hypersensitivity reaction involving lymphokine release from sensitive lymphocytes and appearing 18 to 48 hours after intradermal injection of a drug should also be a good indicator of prior expansion of T cell clones sensitive to that drug. In practice, however, this procedure has not gained widespread use. Also, there is the risk that the intradermal dose of the drug may itself sensitize the patient. The topical application of the drug under a sealed cover (i.e., patch testing) is associated with the same uncertainties. In addition, interpretation of patch testing is complicated by the lack of simple rules and standardized doses and the occurrence of false positive "irritant" responses due to the drug, hyperirritable skin, or extremely high concentrations of the drug. Thus, although sometimes used to detect allergy to topically applied agents, patch testing has not found a place in evaluating allergy to systemically administered drugs.

IN VITRO TESTS

Tests in vitro avoid the anaphylactic and sensitizing hazards of rechallenge or skin testing in vivo. Ideally such tests should also give a precise quantifiable result indicating the type of immunologic reaction (Table 214.2) and its place in the sequentially linked events leading to its clinical expression (Figure 214.1). These ideals can rarely be realized, however, because precise quantifiable kinetic experiments documenting not only the existence of events but also their timing and sequence are few and far between. The modern student of immunology is faced with a myriad of phenomenologic events (B cells, T helper cells, T suppressor cells, immunoglobulin levels, etc.) that are not yet linked into meaningful kinetic sequences that permit precise clinical correlation. Thus, although extensive lists of empiric associations have been compiled, their clinical usefulness is limited at this time.

Thus, the presence of eosinophilia (>15%) is suggestive of allergy providing other causes are ruled out (e.g., parasitic infections, Hodgkin's disease, periarteritis nodosa). It is also possible to quantify *total* serum IgE levels using the PRIST (paper disc radioimmunoassay technique) assay. However, meaningful interpretation of this test requires baseline antibody levels followed by demonstration of a rise correlating with the allergic drug reaction with subsequent decline. This principle is the same as that for serologic diagnosis of infectious diseases except that, by the time the drug reaction occurs, the serum IgE level is usually already raised. Consequently, this test is often of little value. Also the PRIST assay measures *total* IgE and *not* IgE *specific* to the drug responsible for the reaction. Antigen-specific IgE can be measured semiquantifiably using the RAST (radioallergosorbent) assay. This test yields results for penicillin allergy that correlate with the results of skin testing. Few other drug antigens are available that work in this system, and a RAST test is not available for detecting the "minor" determinants of penicillins. Another test that may be of use in the future is release of histamine in vitro following exposure of basophils from the patient to the drug in question. Currently this test is available only as a research tool. The same is still true of plasma (not whole blood) histamine levels.

Other tests that can be of use are the direct and indirect Coombs tests for antibodies (IgG, IgM) and complement on red cells. Hemolysis of red cells by antibody and complement can also be employed in the same context. The complement system can be evaluated by measurement of CH_{50} or of individual complement components. Other tests established in the research laboratory and that may come into clinical application are lymphokine production by lymphocytes and lymphocyte blastogenesis on exposure to antigen. In the lymphokine production test, peripheral blood lymphocytes are obtained from the patient and exposed to the drug (e.g., penicillin) by its addition to the cell culture medium. The supernatant culture medium is then examined for the presence of lymphokines such as macrophage migration inhibitory factor. Another measurable lymphocyte response is the initiation of cell division requiring DNA synthesis as measured by incorporation of radiolabeled (tritiated) thymidine. Drugs to which immunologic reactivity has been demonstrated by this means include nitrofurantoin, antituberculous drugs, phenytoin, and carbamazepine. Apart from the technological difficulties, which make these

tests less than routine, it will be clear from examination of Figure 214.1 that immunologic reactivity to a drug in vitro does not necessarily imply an immunopathologic role. Conversely, a negative test of one aspect of immune reactivity does not exclude an allergic reaction originating at another point in the chain of events.

Clinical Significance

Allergic drug reactions will inevitably occur. They should therefore be anticipated. Patients given a drug with high allergic potential (e.g., penicillin) should remain under supervision for at least 30 minutes after administration. The literature is replete with reports of patients dying of anaphylaxis 20 minutes after leaving the doctor's office. Because the tissue injury is mediated by immunologic reactions to the drug and not by the drug itself, a particular drug cannot usually be implicated from the nature of the allergic events. Consequently, a detailed and often time-consuming drug history is the linchpin of diagnosis, with tests in vivo and in vitro of tertiary importance. In nearly all cases, prevention through avoidance is the only realistic "cure" for recurrences and depends on successful detailed education of the patient or his or her guardians by the physician.

The essence of management of allergic drug reactions lies with the three sequential steps of anticipation, diagnosis, and prevention. Anticipation of all adverse drug reactions is the most crucial of the three. Up to 15% of hospitalized patients will experience an adverse drug reaction. Of these, fewer than 15% will be allergic in nature. Failure to accept these facts is tantamount to wishful thinking and is the main reason why many (>90%) adverse effects pass unrecognized. On the other hand, anticipation places the physician and the patient in the best possible position to diagnose the adverse effects at the earliest warning. The best way to incorporate this into practice is formally to discuss with the patient (or guardians) the risks intrinsic to each drug so that the development of adverse effects can be specifically looked for. A list of what might be observed or felt by the patient or family can be given without being unduly alarmist. The development of an adverse effect that was anticipated and discussed ahead of time gives the clearest possible signal to the patient of the competence of the physician and that events are under control, however unpleasant they may be. The enhanced patient–physician bonding that derives from this process is one of the most satisfying of all professional experiences.

Few specific drugs are available that interrupt the immunologic amplification sequence once it is initiated. Treatment is therefore usually limited to life-supportive measures combined with discontinuance of the drug and administration of antihistamines and nonspecific anti-inflammatory agents such as the corticosteroids. It is for this reason that the considerable time (often hours) invested in obtaining a detailed drug history is so worthwhile. Armed with this information, an intelligent strategy for avoiding the offending agent can often be constructed.

This may not be as simple as telling the patient to avoid a single drug preparation, however. For example, in the case of tartrazine dye sensitivity, a list of tartrazine-containing drugs and foods may be given to the patient. In the case of penicillin allergy, all penicillins should be avoided except in life-threatening situations where no therapeutic alternatives exist, and then only under close supervision. The potential (12%) for cross reactivity in patients with a history of penicillin allergy given cephalosporins should be kept in mind, as should the possibility of cross reactivity among the aminoglycosides. The chemical relationship of "sulfa" drugs (e.g., sulfonamide antibiotics, thiazide diuretics, sulfonylureas) also reemphasizes the need for careful documentation of the chemistry of drug constituents. The same is true of the "caine" family used as local anesthetics and cardiac antidysrhythmics. All this has to be *communicated* (not just articulated) to the patient and family so that they all understand the ramifications of the problem. Patients should be taught to carry a list of potential offending agents and to take responsibility for their allergic diathesis by confronting any new physician with the possibility of an allergic reaction to any proposed drug.

One final form of prevention is desensitization to the drug by administration of incremental doses, starting with extremely low levels. Detailed protocols for different drugs (e.g., penicillin and insulin) can be found in standard allergy texts. Desensitization is undertaken only in extreme situations such as enterococcal endocarditis where urgent penicillin therapy may be mandatory. This should ideally be conducted in an intensive care setting with equipment for resuscitation and continued life support and by physicians experienced in these procedures. Such "desensitization" applies only to Type I reactions and not to the other immunologic mechanisms shown in Table 214.2

Risk of Adverse Reactions

Most drugs employed in human therapeutics have molecular weights below 1000 daltons and are antigenic only when linked covalently as a "hapten" with large molecules (e.g., cell membrane components, proteins, or polysaccharides). As mentioned, drugs such as procainamide may alter nuclear components, rendering them immunogenic to self and resulting in an autoimmune disease resembling systemic lupus. Cephalothin, methyldopa, and mefenamic acid can also alter the red cell membrane so that immunoglobulins adhere nonspecifically. This produces a positive direct Coomb's test but rarely a hemolytic anemia. Drugs given orally have a greater opportunity to be altered by (or combined with) gut flora or their products, absorption mechanisms, and metabolism by the liver. On the other hand, Chase (1946) showed that drugs given by mouth could desensitize the animal to drug administration by other routes. A clinical example of this may be desensitization to penicillin by the oral route. In contrast, topical application carries the highest risk of sensitization, especially if the skin is inflamed. This is a particular hazard for nurses who administer drugs and not infrequently contaminate their hands with the drug.

Other factors, such as genetic endowment and race, probably influence the incidence and type of ADRs, but concrete demonstrations of this are few. Examples include the greater risk of ADRs to isoniazid, hydralazine, and procainamide in slow acetylators, and perhaps to debrisoquine and phenytoin in slow hydroxylators. Atopic patients whose problem seems to involve intrinsic skin, mucosal, and bronchial hyperreactivity do not have an overall increased risk of drug allergy and may actually have less risk of developing contact dermatitis.

The age of the patient may be important inasmuch as children have fewer allergic reactions to drugs, possibly because of less prior exposure. Older patients may have fewer direct allergic reactions to drugs but more autoimmune manifestations, perhaps due to a reduction in helper T cell

function. Clearly, the risk of an allergic reaction increases with prior exposure to the same drug or cross-sensitization with chemically related agents (e.g., with the "caine" local anesthetics). Approximately 12% of patients allergic to penicillin will be allergic to the cephalosporins. A patient who is allergic to one penicillin is to be considered allergic to all penicillins! In general, patients who have experienced one drug reaction have twice the risk (approximately 30%) of developing another, and this probably applies to allergic drug reactions. Finally, underlying disease can influence the development of allergy. For example, patients with hypogammaglobulinemia have fewer antibody-related reactions and patients with sarcoid have less T cell reactivity.

Types of Allergic Drug Reactions

It is customary to divide allergic drug reactions into two clinical categories: systemic and local single organ involvement. From what has been said about mechanisms, it will be clear that all allergic reactions are systemic in nature, although specific organ damage (e.g., asthma, hypersensitivity pneumonia, or hepatitis) or easy visualization (e.g., skin lesions) may suggest a dominant anatomic location. With this in mind, a synopsis of systemic and local allergic drug reactions will be given. More extensive lists can be found in reviews such as that by Cluff et al. (1975), Stewart et al. (1977), and Meyler and Herxheimer (1972). Ongoing reports can be found in periodic reviews such as the Medical Letter, Clin-Alert, and the drug manufacturers' literature.

SYSTEMIC ALLERGIC DRUG REACTIONS

Anaphylaxis. Anaphylaxis, urticaria, and angioedema are examples of Type I reactions. Type I reactions are mediated when mast cells are first sensitized by attachment of the Fc component of IgE molecules, and the Fab components of the same IgE molecules are then cross-linked by bivalent antigen. As a result, the mast cell degranulates with release of mediators such as histamine and SRS-A. Mediator release leads to airway obstruction from edema of the airways and bronchial muscle constriction, contraction of smooth muscle in the gut causing vomiting and diarrhea, uterine contraction with cramps and perhaps vaginal bleeding, and increased vascular permeability with angioedema and urticaria. If the last is severe enough, hypotensive shock may follow with subsequent cardiac dysrhythmias or coma. Death may ensue from laryngeal obstruction alone (usually in children) or in combination with shock and cardiac dysrhythmias.

The diagnosis of anaphylaxis is clinical, and the differential diagnosis includes vasovagal attacks (not unusual after injections), in which the pulse is slow and cyanosis is rare; insulin hypoglycemia attacks; and myocardial infarction, in which there is no airway obstruction. The laboratory has only a minor diagnostic role limited to confirming the complications of anaphylaxis such as hyperinflation on chest x-ray, or ECG and serum enzyme changes (e.g., elevation of serum glutamic oxaloacetic transaminase, creatine phosphokinase, and lactate dehydrogenase. An identical picture can follow release of mediators from mast cells (or basophils) by the so-called complement-derived anaphylotoxins C3a and C5a. Also C5a, in the presence of eicosanoids (leukotriene B_4) and polymorphonuclear leukocytes, causes increased vascular permeability. Furthermore, pharmacologic (i.e., nonimmunologic) induction of mast cell degranulation can also be mediated by drugs such as radiocontrast media and opiates. Thus, the exact sequence of events in individual cases is not always clear.

The incidence of allergic reactions to penicillin is approximately 2%. Nonfatal and fatal anaphylactic reactions to penicillin have been estimated at approximately 0.02% and 0.002% respectively. The percentage risk for other members of the long list of implicated drugs is not documented. Briefly, anaphylaxis has been reported with nearly all antimicrobials, with penicillin chief among them. It is important to note that intradermal Pre-Pen, which is used to test for penicillin allergy, can also cause anaphylaxis. Consequently, such testing should not be undertaken without good reason, and certainly not to satisfy the curiosity of patient or doctor.

The most important aspect of managing anaphylaxis to these and other agents is to take a careful history of drug administration and related past events in the patient and family and to *anticipate* trouble by keeping the patient under observation for at least 30 minutes after drug administration. Finally, an anaphylaxis tray containing epinephrine and equipment for intubation or tracheostomy should be readily available. This is especially the case when desensitization to a drug is being undertaken.

In this context, the immune-like effects of aspirin should be kept in mind. The mechanism underlying these events may relate to the effects of aspirin (and other nonsteroidal anti-inflammatory drugs) on prostaglandin synthesis. Some aspirin-sensitive patients may also exhibit sensitivity to the yellow dye tartrazine, found in many foods and medications.

Serum Sickness Reactions. Serum sickness derives its name from the illness that developed in 95% of patients given 100 ml or more horse serum antitoxins. Use of such horse antitoxins declined with the advent of more vaccines and antimicrobial therapy. But they are still available as antivenoms for snake and spider bites, botulism, gas gangrene, rabies, and diphtheria. The use of rabies human hyperimmune serum should decrease the current risk (16.3%) of serum sickness in patients receiving horse antitoxin.

Serum sickness occurs after the host has begun to make significant amounts of antibody to the horse serum (i.e., past 7 days). The illness is thought to be due to the formation of antigen-antibody immune complexes (i.e., a Type III reaction). The full-blown illness is characterized by fever, urticaria or maculopapular skin rash, splenomegaly, generalized adenopathy, and arthralgia. In view of the presence of circulating immune complexes, which are capable of fixing complement, the occasional occurrence of other features such as generalized vasculitis with purpura, glomerular damage (rare), and neuropathies is easily understood. If the patient has had prior exposure to horse serum (or drug), the onset of serum sickness may be shortened to 2 to 4 days after administration (i.e., an accelerated reaction). Prior exposure to horse serum (or even horse dander) may also precipitate anaphylaxis via a Type I reaction.

Type III reactions may follow administration of many of the same long list of low-molecular-weight and nonprotein drugs that cause Type I reactions. The clinical spectrum is indistinguishable from classic serum sickness. The most frequently implicated drugs at this time are the penicillins. The diagnosis is a clinical one based on the temporal relationship between administration of the drug and development of the illness. In view of its mediation via complement-fixing immune complexes, it is not surprising that the skin and kidney lesions (rare) show immunoglobulin and complement deposits along with infiltration by polymorphonuclear leukocytes (C3a and C5a are chemotactic

for these cells). Similarly, the serum complement level may be reduced and the indirect Coombs test for antibodies to horse serum positive. The disease is self-limiting and usually lasts about a week.

Drug Fever. Drug fever is a not infrequent event complicating and confusing patient management. In the context of treatment of an infectious disease with antimicrobials, the patient's fever gradually subsides only to recur around the end of the first week of therapy. If recognized, cure is achieved by stopping therapy or switching to another antimicrobial. This may be a particular problem in patients on prolonged antimicrobial therapy for serious infections such as endocarditis where there may be few alternative therapeutic choices.

The fever may result from any of the immunologic mechanisms described in Table 214.2 except the Type I reactions. However, tissue-toxic drugs such as amphotericin B may cause fever without an immunologic mechanism. Also, fever is a component of the Jarich–Herxheimer reaction, which follows release of endotoxin from organisms (e.g., *Treponema pallidum)* lysed by the action of the antimicrobial drug (e.g., penicillin).

In the case of drug fever, the temperature may be very high (40°C) and may be accompanied by a polymorphonuclear neutrophil leukocytosis. Despite this, the patient often looks and feels remarkably well. This may be due to release of interleukin I in the absence of local inflammation, bacteremia, or toxemia. Of itself, the illness is benign and resolves spontaneously within a few days of stopping the drug. If the true cause of the fever is not recognized, however, the various immune mechanisms may continue to amplify and manifest themselves in more serious fashion (e.g., exfoliative dermatitis, hepatitis, and vasculitis with tissue necrosis and hemorrhage). Systemic vasculitis (due to immune complex disease) may express itself as hemorrhagic skin lesions (purpura), glomerulitis with proteinuria and hematuria, arthralgias, pulmonary infiltrates, abdominal pain, bleeding from the gut, neuropathy, etc. Currently the penicillins and cephalosporins are the commonest cause of drug fever. However, other causative drugs such as the aminoglycosides, phenytoin, quinidine, procainamide, iodides, and methyldopa may be encountered in a professional lifetime.

Systemic Lupus Erythematosus. Drug-induced SLE was first observed with hydralazine but has since been reported with an increasing number of agents, chief among them procainamide. The drug-induced lupus syndrome has many similarities with the naturally occurring disease (e.g., fever, arthralgias, myalgia, pleurisy, anemia, and skin rashes). However, in the drug-induced disease, the rash and depression of marrow elements (white cells and red cells) are less marked than in natural lupus, pleurisy is less severe, and the kidney is rarely damaged. Also, unlike the natural disease, drug-induced lupus occurs equally in both sexes (SLE has a marked predilection for young women). In terms of pathogenesis it may be that the drugs unmask a latent lupus diathesis. Alternatively it may be that some drugs (e.g., hydralazine, isoniazid), by virtue of their hydrazine group, alter cell nucleoproteins, rendering them immunogenic to self. In keeping with this is the observation that although antinuclear (i.e., antihistone) antibodies occur, antibodies to native DNA are rarely found in drug-induced lupus with the exception of hydralazine-induced disease. Serum complement levels are normal. It is of particular interest that isoniazid and hydralazine have recently been shown to bind covalently with the fourth component of complement (C_4). This leads in turn to diminished solubility and phagocytosis of immune complexes and increased tissue deposition. These observations provide, for the first time, a rational link between the chemical nature of the drug, increased risk of disease in the slow acetylator, and a dominant feature of the disease: immune complex deposition. Other laboratory findings include an elevated erythrocyte sedimentation rate; mild depression of white cell, red cell, and platelet counts; and even a positive LE cell phenomenon in severe cases. A positive Coombs test has been observed with procainamide-induced disease and a false positive syphilis serology with hydralazine.

A partial list of commonly used drugs causing lupus is given in Table 214.3. Of all the drugs shown, procainamide is the most powerful (65%) inducer of antinuclear antibodies, followed by hydralazine. However, a minority of patients with antinuclear antibodies develop clinical SLE but the risk is increased in the slow acetylator. In such individuals, it is desirable to choose antihypertensives other than hydralazine. In procainamide-induced SLE, the absence of antibody to native DNA is a useful discriminator with respect to the natural disease. As drug-induced SLE is more common in slow acetylators, it is of interest that acetylated procainamide may be a less powerful inducer of antinuclear antibodies. Isoniazid induces antinuclear antibody production in 20% of tuberculous patients receiving this drug, but overt lupus is rare. The main treatment is withdrawal of the drug. If the drug has merely unmasked an underlying lupus diathesis, however, more vigorous therapy with steroids may be needed. Of special diagnostic note is SLE induced by D-penicillamine, a drug occasionally used in therapy of rheumatoid arthritis. The latter disease has features in common with SLE and may overlap with it in the same patient.

Insulin Resistance and Allergy. Resistance to insulin is usually nonimmunologic and may be found in disease states such as ketoacidosis, acute infections, and decrease in insulin receptors. Immunologically mediated insulin resistance is rare and may be due to anti-insulin receptor antibodies or antibodies (IgG) to insulin itself. Such resistance usually occurs in the first 12 months after starting insulin. IgG antibodies can also mediate painful local reactions beginning 4 to 6 hours after subcutaneous injection of insulin. These usually appear within a month of starting insulin therapy and spontaneously diminish over the next few weeks. IgE antibodies can also mediate early (<1 h) local reactions,

Table 214.3
Some Agents Associated with Drug-induced Systemic Lupus Erythematosus

Antihypertensives	Hydralazine, methyldopa, reserpine
Anticonvulsants	Carbamazepine, phenytoin, ethosuximide, primidone, troxidone
Antiarrhythmics	Procainamide
Antithyroid	Methylthiouracil, propylthiouracil
Antibacterials	Isoniazid, para-aminosalicylic acid, sulfonamides, penicillins
Others	D-Penicillamine, methysergide, chlorpromazine

urticaria, and even anaphylaxis. This may be a particular risk if insulin is begun, stopped for a period, and then reinstituted. Presumably, the continued daily administration of insulin effectively desensitizes the patient. For this reason, if the patient is seen soon (<48 h) after the reaction, insulin is continued at lower dosages under hospital supervision and the dosage gradually increased. This is, in effect, a combination of therapy with desensitization. If insulin therapy was stopped after the reaction and if insulin therapy is mandatory, then skin testing followed by desensitization is undertaken. Details of such protocols can be found in standard clinical allergy texts. In this context, it should be remembered that the allergic reaction may be due to a non-insulin component in the injection (e.g., protamine or zinc). Hopefully, the availability of human insulin will now revolutionize the prevention and management of these types of problems.

INDIVIDUAL ORGAN INVOLVEMENT

Skin. Probably because it is the largest organ in the body and because it is visible, skin is the most widely recognized (0.3%) site for allergic events. However, it should be reemphasized that most allergic reactions to drugs are, by their very nature, systemic. Also, an allergic reaction to any drug may involve more than one of the immunologic mechanisms shown in Table 214.2. The corollary is that tissue damage is mediated by the available inflammatory and immunologic responses to the drug and not by the drug itself. Thus, many drugs can produce the same clinical reactions, and vice versa. Hence, on its own, inspection of skin lesions does not usually identify the offending drug. This is achieved from a careful history. For the same reasons, exhaustive listings of drugs and clinical classifications of reactions to them are less useful than might be anticipated. A few examples are given in Table 214.4 to illustrate this point. Ampicillin-induced maculopapular rash seems to be a special case in that, in some patients, the rash is not immunologically mediated and may actually disappear despite continued therapy. Also, a very high percentage (>90%) of patients with infectious mononucleosis develop a rash if given ampicillin, a fact that may, in retrospect, be a "diagnostic test" for the disease. In some cases of maculopapular rash and contact dermatitis, however, a Type IV reaction to ampicillin has been implicated, as witnessed by the release of lymphokines from the patient's lymphocytes by penicillin in vitro.

Lungs. The same diagnostic principles described for the skin apply to the detection of pulmonic allergic drug reactions. Because of the greater difficulty of access to lung tissue, the pathogenetic and immunologic definitions of such reactions are even less clear than is the case for skin. However, a number of empiric associations have been made along with putative mechanisms. As before, the division into antigenic and nonantigenic initiation, failure of regulation of immune amplification, and tissue hyperreactivity should be kept in mind.

An example of the last category is propranolol-induced bronchospasm due to beta-adrenergic blockade in the already hyperreactive bronchi of the asthmatic. Given by inhalation, aerosols of polymyxin B, pituitary snuff, cromolyn, and acetylcysteine have also produced attacks of asthma. Whether these effects represent "irritation" of hyperreactive bronchi or specific or nonspecific initiation of immunologic reactivity is hard to say in the individual case. The bronchospastic reactions to acetylcysteine and cromolyn are of particular note, as these drugs may be used in the treatment of asthma. Also of note is asthma induced by nonsteroidal anti-inflammatory agents such as aspirin (the most common), indomethacin, naproxen, etc. These agents seem to disturb the balance between tonic bronchial constriction and dilation by interfering with prostaglandin synthesis. These reactions may be more frequent in patients with nasal polyps. Finally it should always be kept in mind that a non-drug constituent common to many drug formations may cause asthma. The classic example of this is tartrazine dye used to color many medications and foods.

Several drugs have been associated with the appearance of acute inflammatory infiltration of the lung parenchyma. The phenomenon of hypersensitivity pneumonia to inhaled antigens has been well described in the context of farmers lung, bird fanciers lung, etc. Therefore, it is not surprising that similar effects can result from drug administration by inhalation (e.g., bovine pituitary snuff, which has now been replaced by synthetic antidiuretic hormone). Pulmonary infiltrates with eosinophilia (PIE syndrome) have been associated with penicillins, sulfonamides, and cromolyn. An acute interstitial pneumonitis characterized by dyspnea, cough, pleuritic pain, and fever can occur with nitrofurantoin. Physical examination may reveal rales, but the chest x-ray may be negative unless the inflammatory process is severe, in which case cyanosis may appear and lung function tests reveal a restrictive pattern. Eosinophilia may or may not be present. The process may begin anywhere from a few hours

Table 214.4
A Partial List of Drugs Causing Allergic Manifestations in the Skin

Maculopapular rash	Ampicillin, sulfonamides, isoniazid, phenytoin, allopurinol, gold
Angioedema and/or urticaria	Penicillins, cephalosporins, sulfonamides, insulins, iodine, and radiocontrast media
Contact dermatitis	Penicillins, sulfonamides, local anesthetics, aminoglycosides, antihistamines; also ethylenediamine stabilizer or parabens preservatives in skin creams used to treat dermatitis!
Erythema multiforme and Stevens–Johnson syndrome	Penicillins, sulfonamides
Toxic epidermal necrolysis	Penicillins, sulfonamides, sulfones, barbiturates, phenytoin, isoniazid, allopurinol
Erythema nodosum	Penicillins, sulfonamides, salicylates, oral contraceptives
Exfoliative dermatitis	Gold, penicillins, sulfonamides, barbiturates, allopurinol, phenothiazines
Purpura (due to vasculitis or thrombocytopenia)	Sulfonamides, barbiturates, gold, antihistamines, iodides
"Fixed" drug eruption (i.e., lesions recurring in the same anatomic sites)	Phenolphthalein, barbiturates, sulfonamides, tetracycline, analgesics, gold
Photo-allergic (i.e., eczematous)[a]	Sulfonamides, diuretics, hypoglycemics, phenothiazines

[a] *Phototoxic* reactions (e.g., to doxycycline) are not allergic in nature but due to oxidative tissue injury secondary to light activation of the drug in the skin. The skin lesion resembles sunburn with vesiculation.

to several days after nitrofurantoin is started, improves within 1 to 2 days after cessation, and recurs if the drug is reintroduced.

A more chronic type of fibrotic infiltrate of the lung has also been observed with nitrofurantoin. The onset is insidious and begins months after starting the drug with dyspnea, cough, and cyanosis in severe cases. Some other drugs which can have similar fibrosing effects include phenytoin, carbamazepine, bleomycin, busulfan, cyclophosphamide, and methysergide. Methysergide can also produce pleural or retroperitoneal fibrosis. At present, it is debated if these are immunologic events or represent a secondary fibrotic reaction to oxidative injury to the tissues by the drugs. In the case of methotrexate, there may be an initial acute granulomatous reaction suggestive of immunologic reactivity. This often subsides even if methotrexate is continued, although the process may go on to pulmonary fibrosis. Drugs which induce the lupus syndrome can also produce fibrosis (e.g., hydralazine, procainamide, isoniazid).

Blood Components. Pharmacologic and idiosyncratic drug reactions such as primaquin-induced hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficiency and chloramphenicol-induced aplastic anemia have already been alluded to (Table 214.1). From Table 214.2 it is clear that the various cells of the blood can be targets for immunologic attack just like any other cell in the body, although the precise immunologic mechanism in any one disease may not be clear. The most commonly identified mechanisms are Type II and Type III reactions. In Type II reactions, the drug binds to the cell as a hapten to which antibody then adheres. In a Type III reaction, the drug binds to a serum protein to which antibody is formed, leading to the formation of cytolytic antigen–antibody–complement complexes, which then lyse cells with which they happen to come in contact (i.e., an "innocent bystander" reaction).

Examples include sedormid- or quinidine-induced thrombocytopenia. The list of other drugs causing this type of reaction is very long, and the diagnosis is made in the context of thrombocytopenia associated with drug administration followed by a literature search beginning with the manufacturer's description of the drug. Of particular note is thrombocytopenia induced by heparin, which may complicate anticoagulant therapy. Other hemorrhagic features, such as gastrointestinal bleeding, hematuria, and purpura, are merely secondary to the thrombocytopenia and offer no specific diagnostic clues. Laboratory tests such as complement fixation and platelet factor III release or release of chromium 51 from radiolabeled platelets have been used. However, negative tests do not exclude the diagnosis and are of subsidiary diagnostic value to the history and response to withdrawal of the drug. Rechallenge is almost invariably unjustified.

Immunologically mediated lysis of red cells (i.e., hemolytic anemia) follows the same principles as those for thrombocytopenia. Thus, adherence of penicillin to the red cell as a hapten with subsequent adsorption of antibody (Type II reaction) may lead to removal of the cell by the spleen or, less commonly, by complement lysis. The direct Coombs test may reveal IgG adhering to the red cells. Complement-fixing immune complex (i.e., Type III) reactions by drugs such as quinidine and sulfonamides may also occur. As expected, the direct Coombs test often detects complement on the red cell surface although the Coombs test for immunoglobulin may be negative. The latter observation may indicate light binding of immunoglobulin (e.g., IgM) which may "hop" from red cell to red cell, activating cytolytic complement on the surface of each in turn and producing a degree of hemolysis out of proportion to the amount of circulating antigen-antibody complexes. Not all patients with a positive Coombs test actually develop hemolytic anemia, however.

Another important drug that can induce hemolytic anemia is methyldopa. The mechanism is controversial but may involve alteration of the red cell membrane with secondary development of autoimmune antibody. Alternatively, the methyldopa may alter existing IgG so that it adheres to red cells. Whichever mechanism applies, a positive Coombs test develops in up to one-third of patients in the first 6 months of therapy. Only a minority (<1%) of such patients actually develop hemolytic anemia, however, so stopping the drug is usually not necessary. A similar phenomenon has been described with L-dopa.

In a similar vein, cephalosporin drugs can alter the red cell membrane so that serum proteins adhere and the direct Coombs test becomes positive. Hemolysis does not occur, but false agglutination may be encountered in cross-matching of blood for transfusion. Like the penicillins, with which there is some cross reaction, cephalosporins may also produce a hapten type of positive Coombs test.

Agranulocytosis may result from the slow onset of toxic effects of drugs. A rapid onset of agranulocytosis via immunologic mechanisms (e.g., Type III or "innocent bystander") usually appears within 7 to 10 days of starting therapy. Again the list of drugs is a long one which is not usefully reproduced here. Examples include sulfa drugs, phenothiazines, antithyroid drugs, quinine, and hydralazine. In any one case, the manufacturer's literature and other encyclopedic sources should be referred to (see the references).

Liver. Allergic drug reactions involving the liver are even less well defined than those in the lung and are inferred when liver damage occurs in the context of systemic manifestations such as fever, adenopathy, skin rash, or eosinophilia. As in the lung, damage may be focused in the parenchyma or ducts of the organ. Cholestatic occlusion of the ducts has been described with the phenothiazines, imipramine, and the urinary antiseptics nalidixic acid and nitrofurantoin. The erythromycins have also been implicated, especially the estolate preparation. As could be anticipated from obstruction of the bile ducts, alkaline phosphatase is raised and liver biopsy shows cholestasis with some periportal infiltrate with eosinophils and mononuclear cells. Parenchymal hepatocellular damage resembles that of viral hepatitis, with fever, eosinophilia, and rash.

Some of the drugs implicated include the hydrazine monoamine oxidase inhibitors, phenytoins, quinidine, methyldopa, and the antituberculous drugs isoniazid, rifampin, and pyrazinamide. A drug of special interest is the anesthetic halothane, which can cause eosinophilic granulomas in the liver. The risk of reaction to halothane may increase with prior exposure, which also supports a possible immunologic pathogenesis. However, whether the immunologic response actually initiates the damage or merely represents an immunologic reaction to damaged tissue is controversial.

Kidney. In view of what has already been said about drug-induced immune complex disease, it might be anticipated that glomerular damage would be a common sequel. But this has been well documented with only a few drugs such as captopril. Glomerulitis with or without pulmonary base-

ment membrane damage with hemorrhage (i.e., Goodpasture's syndrome) has also been reported with D-penicillamine. Even in drug-induced SLE, glomerular damage is rare. In contrast, allergic interstitial nephritis is not uncommon and has been reported with penicillins, cephalosporins, phenytoin, sulfa drugs, thiazides, and rifampin. The classic cause is methicillin with accompanying fever, rash, and eosinophilia. The renal biopsy reveals interstitial nephritis, which explains the development of renal insufficiency, proteinuria, and the presence of red cells and white cells in the urine. Immunologic staining may reveal penicilloyl determinants, immunoglobulin, and complement on the basement membrane. In addition, there may be a positive skin test to penicillin and lymphocytic proliferation in vitro in response to methicillin, suggesting a Type IV reaction.

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